Sounding Board

Is Placebo Surgery Unethical?

SURGICAL procedures are often introduced into practice without rigorous evaluation. Moreover, clinical trials of surgery have seldom included placebo surgery as a control, owing to ethical concerns. In 1959, the *Journal* published the results of a placebo-controlled trial of ligation of the internal thoracic artery for the treatment of angina.[1] In this issue of the *Journal,* Moseley et al. report on a placebo-controlled trial of arthroscopic surgery for osteoarthritis of the knee.[2] In both studies, the surgical interventions were no more effective than placebo operations. A major difference between the use of placebo surgery 43 years ago and its use now, however, is the degree of attention to the ethical aspects of conducting clinical research.

THE ETHICS OF CLINICAL RESEARCH

The idea of using placebo surgery is apt to elicit an immediate negative judgment, because it appears to violate the fundamental ethical principles of beneficence and nonmaleficence.[3] Doctors should not expose patients to risks if there is no prospect of possible benefits. With respect to surgery, this means that surgeons should not invade the body except for the purpose of cure or amelioration. In a recent ethical critique of placebo surgery for Parkinson's disease, Clark asserted, "The researcher has an ethical responsibility to act in the best interest of subjects."[4]

Although this statement reflects a commonly articulated moral stance with regard to clinical research, it confounds the ethics of clinical research with the ethics of clinical care. The randomized, controlled trial is not a form of individualized medical therapy; it is a scientific tool for evaluating treatments in groups of research participants, with the aim of improving the care of patients in the future. Clinical trials are not designed to promote the medical best interests of enrolled patients and often expose them to risks that are not outweighed by known potential medical benefits. Accordingly, the use of placebo surgery must be evaluated in terms of the ethical principles appropriate to clinical research, which are not identical to the ethical principles of clinical practice.[5]

Clinical research involves an inherent tension between the ethical values of pursuing rigorous science and protecting participants from harm.[6] To avoid exploiting research subjects, clinical trials must satisfy several ethical requirements.[5] Clinical trials are unethical if they are not designed to answer valuable scientific questions with the use of valid research methods. In addition to having scientific merit, clinical trials must present a favorable risk–benefit ratio: the risks to participants must be minimized and justifiable by the benefits to them, if any, and the potential value of the scientific knowledge to be gained from the study. Finally, investigators must obtain informed consent from participants.

Use of an invasive procedure as a placebo control poses risks to research subjects assigned to the control group, without the prospect of a benefit from their participation, and the burden of proof is therefore on those who argue that placebo surgery is warranted as a means of evaluating the efficacy of surgical procedures. The use of placebo surgery in clinical trials raises three key ethical questions. First, is placebo surgery compatible with the ethical requirement to minimize risks? Second, are the risks associated with placebo surgery reasonable and justifiable in relation to the potential value of the scientific knowledge to be gained from its use? Third, can informed consent be obtained for a trial that randomly assigns patients to undergo genuine or placebo surgery?

PLACEBO SURGERY

Minimizing Risks

Placebo-controlled trials of medical agents involve the administration of inert substances disguised as active medication. Trial participants do not incur risks by taking the placebo pill, but they may be at risk for clinical deterioration or lack of improvement because they are not receiving an active therapeutic agent. In contrast, participants in a placebo-controlled trial of surgery are exposed to risks from the placebo procedure itself.

Macklin argued that placebo surgery violates "an essential standard for research: the requirement to minimize the risk of harm to subjects."[7] The ethical requirement to minimize risks in randomized, controlled trials must be considered in the context of alternative study designs for answering scientific questions about the efficacy of treatment. Can a valid evaluation of a given surgical intervention be conducted without the use of a placebo control, thus minimizing risks without compromising scientific rigor?

In the trial of arthroscopic knee surgery reported by Moseley et al., the primary outcome measure was pain, an inherently subjective phenomenon. It is doubtful that valid data could be obtained from a randomized clinical trial that compared a group of patients assigned to undergo arthroscopic surgery with a control group that received no treatment. Because patients enrolled in such a trial would obviously know whether or not they had undergone surgery, their reports of pain

might be biased. In reporting the degree of knee pain and function, patients might be influenced by their expectation of improvement after surgery and postoperative care. Furthermore, assessment of the outcome without knowledge of the treatment assignments would require that patients not disclose the treatment they had received — an unlikely prospect.

In addition to the possibility of biased evaluations of outcomes, a trial that compares surgery with no treatment or with standard medical treatment does not control for the placebo effect of surgery.[8] Reduced pain and improved function may result from the invasiveness of the procedure and the belief that one is undergoing surgery, rather than from any specific effects of surgery. A recent meta-analysis called into question the power of the placebo effect,[9] but that analysis did not include trials of surgery. Furthermore, the outcome variable that was most suggestive of a true placebo effect was pain. There is reason to believe that the invasiveness of surgery may be associated with a pronounced placebo effect.[10-13]

These methodologic considerations lead to the conclusion that a placebo control is required for a rigorous scientific evaluation of surgery when the primary outcome is a subjective phenomenon such as pain or the quality of life.[14] If a placebo control is necessary for a valid test of the efficacy of a surgical procedure, then use of placebo surgery does not contravene the requirement of minimizing risks. In this case, there is no alternative to a placebo control; no other sufficiently rigorous study design poses less risk.

In addressing the issue of minimizing risks, one must consider not only the question of whether placebo surgery is methodologically necessary but also the question of whether the risks of placebo surgery can be reduced. Moseley et al. reduced the risks of the placebo surgery in their trial by using a short-acting tranquilizer combined with an opioid for anesthesia, which is less risky than general anesthesia with endotracheal intubation, the standard form of anesthesia used in patients undergoing arthroscopic surgery.

Justifying Risks

Even if the risks of a scientifically valuable and valid clinical trial have been minimized, it does not follow that they are justified. Critics of placebo surgery have argued that it exceeds an acceptable threshold of risk for subjects who are randomly assigned to undergo the invasive intervention merely as a scientific control.[4,15] These subjects are exposed to substantial risks without the prospect of possible benefits.

Can the potential value of the knowledge to be gained from a well-controlled trial involving the use of placebo surgery justify the risks to the participants? It is clearly unethical to jeopardize severely the health and well-being of research subjects only for the good of future patients. In the trial of arthroscopic surgery reported by Moseley et al., the risks for subjects who were randomly assigned to the placebo group included potential harm from three skin incisions and from anesthesia. These risks are certainly greater than minimal, but they do not substantially exceed the risks of other generally accepted research interventions, such as muscle biopsy, bronchoscopy, and phase 1 testing of experimental drugs in healthy volunteers, which do not offer participants a prospect of direct benefits. The trial of arthroscopic surgery posed considerably less risk to participants in the placebo group than did the controversial placebo-controlled trial of a cellular-based treatment for Parkinson's disease, which involved the drilling of burr holes in the skull and the administration of general anesthesia, intravenous antibiotics, and low doses of cyclosporine.[16]

Informed Consent

Why would subjects volunteer for a clinical trial if they understood that they might undergo placebo surgery? Empirical studies of informed consent in clinical trials involving patients with psychiatric disorders and those with cancer have shown evidence of a "therapeutic misconception" about research.[17,18] Many research participants appear to confuse treatment in the scientific context of clinical trials with individualized medical care. There is also evidence that they overestimate the benefits of participation in a trial and underestimate the risks.[18] These deficits in understanding make it difficult to obtain meaningful informed consent. Problems with informed consent are of particular concern in studies involving interventions that depart substantially from standard clinical practice, especially if the risks of these interventions, such as placebo surgery, are substantial.[4,7] There is also concern about the enrollment of "vulnerable" subjects — those who may have an impaired capacity to give informed consent or who may be susceptible to "undue inducement" to participate in research.[19]

We see no reason for special concern about informed consent in the trial conducted by Moseley et al. Osteoarthritis of the knee is a painful and potentially debilitating condition, but it is not life-threatening. Nor is it associated with impaired decision-making capacity. Moseley et al. report that enrolled patients were required to write in their charts that they understood that they might undergo an invasive placebo procedure that would not involve potentially beneficial treatment of their arthritis. The fact that 44 percent of the eligible patients declined participation indicates that the enrolled subjects decided to participate in the trial without undue inducement or coercion.

An additional ethical concern about obtaining in-

formed consent for participation in trials that involve placebo surgery is the use of communication and actions designed to give the false impression that subjects randomly assigned to placebo surgery have undergone a real surgical procedure.[7] Because of the possibility that some patients might remain conscious during the placebo surgical procedure in the study by Moseley et al., it was performed to resemble arthroscopic débridement. The report does not state whether the plan to use a placebo intervention that mimicked arthroscopic débridement was disclosed to prospective subjects as part of the informed-consent process. Such a practice can be ethical if investigators inform prospective participants that it will be used to maintain the blinded condition and if they reveal the nature of the deception at the end of the study.[20]

CONCLUSIONS

Reasonable people are bound to differ over the ethics of a controversial practice such as the use of placebo surgery in clinical trials. Ethical objections — based on the requirements to minimize risks, limit the level of risks that are not offset by the potential benefits to participants, and obtain informed consent — do not support an absolute prohibition against the use of placebo surgery when its use is methodologically necessary to answer clinically important questions. Indeed, we suggest that the trial conducted by Moseley et al. exemplifies the ethically justified use of placebo surgery. Each proposed trial involving placebo surgery must be evaluated carefully in the light of these ethical considerations.

A full ethical assessment must include consideration of the consequences of not conducting rigorous trials of surgery. Arthroscopic surgery has become a common treatment for osteoarthritis of the knee in the absence of rigorous scientific evaluation of its efficacy. According to data cited by Moseley et al., the costs of this intervention are approximately $3.25 billion per year. Yet the results of this important study demonstrate that two methods of arthroscopic surgery are no more effective than a placebo operation. Thus, patients have been exposed to risks and third-party payers have incurred substantial costs for a treatment that offers no benefit to the patient. Trials of surgical procedures that include the use of placebo surgery should be conducted before the procedures become standard treatments, provided that these trials meet the ethical requirements that are appropriate for clinical research.

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